Epidemiological Risk Factors for Isolation of Ceftriaxone-Resistant versus -Susceptible *Citrobacter freundii* in Hospitalized Patients

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Antimicrobial resistance is an emerging problem among nosocomial bacteria. Risk factors for the recovery of ceftriaxone-resistant (CRCF) or -susceptible (CSCF) *Citrobacter freundii* in clinical cultures from hospitalized patients were determined by using a case-case-control study design. CRCF was isolated from 43 patients (case group 1) and CSCF was isolated from 87 patients (case group 2) over a 3-year period. Risk factors for CRCF were exposure to imipenem (odds ratio [OR], 7.5; 95% confidence interval [CI], 1.2 to 45.4), broad-spectrum cephalosporins (OR, 6.9; 95% CI, 1.8 to 26.7), vancomycin (OR, 3.0; 95% CI, 1.2 to 7.4), or piperacillin-tazobactam (OR, 2.6; 95% CI, 1.1 to 6.2), as well as hospital length of stay ≥1 week (OR, 3.6; 95% CI, 1.3 to 10.2) and intensive care unit (ICU) stay (OR, 2.6; 95% CI, 1.1 to 6.2). Risk factors for CSCF were peripheral vascular disease (OR, 23.2; 95% CI, 4.3 to 124.6), AIDS (OR, 9.5; 95% CI, 1.6 to 55.5), cerebrovascular disease (OR, 4.2; 95% CI, 1.6 to 10.8), and ICU stay (OR, 3.1; 95% CI, 1.8 to 5.4).

The health care system has been greatly impacted by the emergence of antibiotic-resistant gram-negative infections (26), and according to the Centers for Disease Control and Prevention's National Nosocomial Infections Surveillance (NNIS) System, the incidence of nosocomial infections caused by antibiotic-resistant gram-negative pathogens is increasing (34). For example, in 2000, broad-spectrum cephalosporin resistance among *Pseudomonas aeruginosa* and *Escherichia coli* increased 24 and 15%, respectively, compared with the mean resistance rate over the previous 5-year period of 1995 to 1999 (34). Antibiotic-resistant pathogens compromise the treatment of hospitalized patients with serious infections (26), and the literature is replete with evidence that the presence of antibiotic-resistant *Enterobacteriaceae* is associated with longer hospital stays, greater use of additional antibiotics, and higher mortality (6, 11, 13, 20, 22).

Among the more serious antimicrobial resistance issues facing hospitals is that of *Enterobacteriaceae* resistant to broad-spectrum cephalosporins (3, 4, 12, 36, 37, 39, 40, 42). Beta-lactamases capable of producing resistance to broad-spectrum cephalosporins were initially reported in Germany in 1983 (28). Resistance rates rose sharply as the use of broad-spectrum cephalosporins increased, particularly between 1985 and 1989, with some regional and national variation (25).

Citrobacter species are an important cause of nosocomial infections, particularly involving the urinary and respiratory tracts of hospitalized patients. They have also been associated with intra-abdominal infections, meningitis, and hospital-acquired bacteremias (1, 5, 7, 9, 10, 16, 23, 30, 31, 41). Among *C. freundii* isolates, resistance to broad-spectrum cephalosporins

(ceftriaxone and ceftazidime), piperacillin, and piperacillin-tazobactam has been reported to be between 39.1 and 47.8% and may be increasing (4, 36, 39, 40, 44). Resistance to broad-spectrum cephalosporins was highest in the northeast and southwest (50%) (36).

The aim of this study was to identify risk factors for the nosocomial isolation of ceftriaxone-resistant *Citrobacter freundii* (CRCF) and ceftriaxone-susceptible *Citrobacter freundii* (CSCF) from clinical specimens. Risk factors of particular interest were prior exposures to antimicrobial agents. To our knowledge, this is the first study that sought to identify risk factors for the isolation of CRCF and CSCF.

MATERIALS AND METHODS

Case definition, control definition, and study design. A case-case-control study design was used (20, 22, 27). The study was performed at the University of Maryland Medical System, a tertiary care hospital with 609 beds, including the R. Adams Cowley Shock Trauma Center and the Greenbaum Cancer Center. The first group of cases consisted of patients with nosocomial, clinical cultures that grew CRCF. The second group of cases consisted of patients with nosocomial, clinical cultures that grew CSCF. The term "nosocomial" refers to cultures drawn at least 48 h after admission to the hospital and thus theoretically not associated with an infection present prior to admission. The term "clinical" refers to cultures drawn in search of infection as an etiology for patient deterioration.

The microbiology laboratory database was electronically searched to identify all nosocomial, clinical cultures positive for *C. freundii* from patients admitted between October 1997 and January 2000. Patients with *C. freundii* isolates obtained within the first 48 h of admission (potentially community acquired) were excluded, as were isolates obtained from surveillance cultures. Patients admitted for less than 48 h were also excluded from the control groups. The control group for the CRCF cases consisted of patients who had been admitted to the same service in the same period of time as CRCF patients (frequency-matched controls). Patients in the control group for the resistant cases did not have CRCF isolated during their hospitalization. We attempted to select approximately six controls for each CRCF patient. The control group for the susceptible cases was identical to the control group for the resistant cases, with the exception that patients with CSCF were also excluded.

The advantage of the case-case-control design was that it permitted the simultaneous identification of risk factors for the isolation of CRCF and CSCF. The

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TABLE 1. Bivariate risk factors for the isolation of CRCF

Risk factor	Control patients (n = 250)		Case patients (n = 43)		P value	OR[b]	95% CI[b]
	n (%)	[IQR] or SD[a]	n (%)	[IQR] or SD[a]			
Demographic							
Age (mean yr)	50.8	16.7	51.1	16.3	0.91		
Gender (% female)	144 (58)		29 (67)		0.24	1.52	0.77–3.03
Comorbid conditions							
AIDS	3 (1)		2 (5)		0.16	4.02	0.65–24.77
Cardiac disease							
Heart failure	24 (10)		1 (2)		0.14	0.22	0.03–1.70
Post-myocardial infarction	13 (5)		0 (0)		0.23	0.20*	0.01–3.46*
Peripheral vascular disease	2 (1)		2 (5)		0.10	6.05	0.83–44.15
Diabetes	34 (14)		6 (14)		1.00	1.03	0.40–2.63
Malignancy	30 (12)		9 (21)		0.14	1.94	0.85–4.44
Cerebrovascular injury	10 (4)		2 (5)		0.69	1.17	0.25–5.54
Hepatic disease							
Mild liver disease	10 (4)		4 (10)		0.13	2.46	0.74–8.24
Severe liver disease	4 (2)		2 (5)		0.21	3.00	0.53–16.91
Renal disease	8 (3)		0 (0)		0.61	0.33*	0.02–5.79*
Charlson comorbidity score (mean)	1.5	2.0	2.2	2.6	0.10		
Related to hospitalization							
Time at risk, median days	6	[4–9]	21	[10–38]	<0.0001		
ICU stay	82 (33)		33 (77)		<0.0001	6.76	3.18–14.39
Surgery	14 (18)		8 (19)		1.00	1.01	0.44–2.33
Admissions in past yr (mean)	0.6	1.2	1.3	1.6	0.01		
Transfer	32 (13)		13 (30)		0.01	2.95	1.40–6.24
Antibiotic use							
Any antibiotic	185 (74)		43 (100)		<0.0001	30.72*	1.86–506.13*
Imipenem	4 (2)		6 (14)		<0.0001	9.97	2.69–37.02
Piperacillin-tazobactam	34 (14)		21 (49)		<0.0001	6.06	3.02–12.2
Ampicillin-sulbactam	25 (10)		7 (16)		0.29	1.75	0.71–4.34
Vancomycin	24 (10)		20 (47)		<0.0001	8.19	3.94–17.03
Cephalosporin							
Narrow spectrum	79 (32)		15 (35)		0.72	1.16	0.59–2.29
Expanded spectrum	16 (6)		10 (23)		<0.01	4.43	1.86–10.58
Broad spectrum	11 (4)		7 (16)		0.01	4.22	1.54–11.60
Cefepime	6 (2)		3 (7)		0.13	1.29	0.81–2.05
Macrolide	10 (4)		4 (9)		0.13	2.46	0.74–8.24
Aminoglycoside	59 (24)		18 (42)		0.02	2.33	1.19–4.57
Quinolone	54 (22)		14 (33)		0.12	1.75	0.87–3.55

[a] [IQR] or SD, interquartile range or standard deviation, respectively, for continuous variables.
[b] An asterisk indicates approximation. The logit estimator used a correction of 0.5 in every cell of those tables that contained a zero.

study generated two multivariable models. The first model identified risk factors for CRCF compared to patients from the same medical or surgical services, and the second model identified risk factors for CSCF. As with other case-case-control studies, the control population consisted of all patients potentially at risk for developing the infection, not just those already infected with susceptible strains. Additional advantages of this study design have been outlined in previous publications (21, 27).

Risk factors investigated. Data were collected from administrative, pharmacy, and laboratory computerized databases by means of a relational database management system. The relational database is maintained by the Information Technology Group at the University of Maryland. Pharmacy, microbiology, and medical demographics tables in the relational database have been validated directly from medical records for over 400 patients admitted between October 1997 and January 2000. In addition, data from 10% of the cases and 5% of the controls in this study were validated directly from medical charts. The positive and negative predictive values of the data from the databases were calculated to be greater than 99%.

Variables explored as possible risk factors included age, gender, intensive care unit (ICU) stay prior to the outcome of interest, surgery prior to the outcome of interest, transfer from another hospital, number of admissions to our hospital in the prior year, length of hospital stay prior to the outcome of interest (for cases,

length of stay prior to *C. freundii* isolation, and for controls, the complete length of stay), treatment with antimicrobial drugs analyzed individually and in groups, underlying diseases or comorbid conditions, and the Charlson score (8) (the last two obtained by using coding of the International Classification of Diseases, version 9 [8]) (Tables 1 and 2).

Only data on antimicrobial agents received within the hospital were analyzed. For the cases, treatment with antimicrobials was included in the analysis only when the agents were given within 14 days of isolation of CRCF for case group 1 and within 14 days of isolation of CSCF for case group 2. For controls, treatment with antimicrobial agents during the 14 days prior to discharge was analyzed. The rationale behind the choice of 14 days was to avoid analyzing antibiotics that patients had received during the initial phase of a lengthy admission. For example, if a patient had been admitted for 40 days prior to the nosocomial isolation of the organism, we believed that the antibiotics received early in the admission were less likely to be related to the isolation of *C. freundii* than those received within 14 days.

The median length of stay was 6 days in the control population. Length of stay was analyzed by dividing the patients into two groups: (i) those with a length of stay of ≥7 days and (ii) those with a length of stay of <7 days. This was done because the variable, length of stay, was not normally distributed and was not

TABLE 2. Bivariate risk factors for the isolation of CSCF

Risk factor	Control patients ($n = 248$)		Case patients ($n = 87$)		P value	OR	95% CI[b]
	n (%)	[IQR] or SD[a]	n (%)	[IQR] or SD[a]			
Demographic							
Age (mean yr)	50.8	16.7	53.6	16.7	0.18		
Gender (% female)	144 (58)		43 (49)		0.17	0.71	0.43–1.15
Comorbid conditions							
AIDS	2 (1)		4 (5)		0.04	5.93	1.07–32.96
Cardiac disease							
Heart failure	23 (9)		15 (7)		0.05	2.04	1.01–4.11
Post-myocardial infarction	13 (5)		5 (6)		0.79	1.10	0.38–3.19
Peripheral vascular disease	2 (1)		10 (11)		<0.0001	15.97	3.43–74.48
Diabetes	33 (13)		20 (33)		0.04	1.94	1.05–3.61
Malignancy	30 (12)		10 (11)		1.00	0.94	0.44–2.02
Cerebrovascular injury	10 (4)		14 (16)		<0.001	4.56	1.95–10.71
Hepatic disease							
Mild liver disease	10 (4)		1 (1)		0.30	0.28	0.03–2.19
Severe liver disease	4 (2)		1 (1)		1.00	0.71	0.08–6.43
Renal disease	8 (3)		0 (0)		0.12	0.16*	0.01–2.83*
Charlson comorbidity score (mean)	1.5	2.0	2.1	2.0	0.001		
Related to hospitalization							
Time at risk (median days)	5.5	[4–9]	7	[4–11]	0.42		
ICU stay	81 (33)		52 (60)		<0.0001	3.06	1.85–5.07
Surgery	46 (19)		18 (21)		0.64	1.15	0.62–2.11
Admissions in past yr (mean)	0.6	1.2	1	1.6	<0.01		
Transfer	32 (13)		19 (22)		0.05	1.89	1.00–3.54
Antibiotic use							
Any antibiotic	183 (74)		69 (79)		0.39	1.36	0.75–2.46
Imipenem	4 (2)		3 (3)		0.38	2.18	0.48–9.93
Piperacillin-tazobactam	33 (13)		18 (21)		0.12	1.70	0.90–3.21
Ampicillin-sulbactam	23 (9)		9 (10)		0.83	1.13	0.50–2.54
Vancomycin	24 (10)		11 (13)		0.42	1.35	0.63–2.89
Cephalosporin							
Narrow spectrum	78 (31)		29 (33)		0.79	1.09	0.65–1.83
Expanded spectrum	16 (6)		3 (3)		0.42	0.52	0.15–1.82
Broad spectrum	11 (4)		4 (5)		1.00	1.04	0.32–3.35
Cefepime	3 (1)		0 (0)		0.57	0.74	0.69–0.79**
Macrolide	9 (4)		1 (1)		0.46	0.31	0.04–2.47
Aminoglycoside	58 (23)		14 (16)		0.17	0.63	0.33–1.20
Quinolone	54 (22)		9 (10)		0.02	0.41	0.20–0.88

[a] [IQR] or SD, Interquartile range or standard deviation, respectively, for continous variables.
[b] An asterisk indicates approximation. The logit estimator used a correction of 0.5 in every cell of those tables that contained a zero.

linear across the outcome and therefore could not be placed in the logistic regression analysis as a continuous variable.

Statistical analyses. All statistical analyses were performed with SAS software, version 8 (SAS Institute, Cary, N.C.). Bivariate analyses were performed separately for each of the variables. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for categorical variables. P values were calculated by the Fisher's exact test for categorical variables and by the Student's t test or the Wilcoxon rank-sum test for continuous variables.

Variables with a P value of <0.1 in the bivariate analyses were included in the logistic regression model for the multivariable analysis. Backward selection processes were utilized. Risk factors were checked for confounding, collinearity, and interaction. Confounders were included in the multivariable models if covariate inclusion changed the coefficient of any statistically significant variable in the logistic regression model by 10% or greater. All tests were two tailed, and a P value of ≤0.05 was considered significant.

RESULTS

During the 3-year study period, 43 patients with CRCF (case group 1) and 87 patients with CSCF (case group 2) were identified. A total of 250 control patients were included in control group 1. Of these control patients, two had CSCF isolated during hospitalization and therefore were not included in control group 2 ($n = 248$).

Clinical cultures of CRCF were most often recovered from urine samples (51%). CRCF was also isolated from the following sites: peritoneal fluid or other intra-abdominal sources (26%), sputum (12%), catheter tips (5%), wound specimens (5%), and blood (2%). CSCF was cultured from urine samples (49%), wound specimens (21%), sputum (17%), blood (7%), peritoneal fluid or other intra-abdominal sources (5%), and catheter tips (1%). The services on which patients with CRCF and CSCF were receiving care on the date the positive culture result was obtained included medicine (19 and 17%, respectively), surgery (19 and 25%, respectively), trauma (19 and 23%, respectively), transplant service (28 and 21%, respectively), and hematology or oncology (9 and 8%, respectively).

The results of bivariate analysis of risk factors for CRCF are outlined in Table 1. Risk factors for CRCF that were found to

TABLE 3. Multivariable analysis of risk factors for CRCF

Risk factor	Estimate[a]	Standard error[b]	P value	OR (95% CI)
Imipenem	2.01	0.92	0.03	7.5 (1.2–45.4)
Broad-spectrum cephalosporins	1.93	0.69	0.005	6.9 (1.8–26.7)
Vancomycin	1.11	0.45	0.01	3.0 (1.2–7.4)
Piperacillin-tazobactam	0.94	0.45	0.03	2.6 (1.1–6.2)
Hospital length of stay >6 days	1.27	0.53	0.02	3.6 (1.3–10.2)
ICU stay	0.96	0.44	0.03	2.6 (1.1–6.2)

[a] Intercept, −3.81.
[b] Intercept, 0.48.

be statistically significant in the bivariate analysis included length of stay in the hospital of ≥7days, ICU stay, previous hospital admissions in the past year, and transfer from another hospital. Exposure to antibiotics in general was a significant risk, and exposure to each of the following individual antibiotics in the 14 days prior to the isolation of CRCF also posed a significant risk: imipenem, piperacillin-tazobactam, vancomycin, expanded-spectrum cephalosporins, broad-spectrum cephalosporins, and aminoglycosides.

Risk factors for CSCF found in the bivariate analysis are outlined in Table 2. They included the following comorbid conditions: AIDS, heart failure, peripheral vascular disease, diabetes, cerebrovascular injury, and higher Charlson comorbidity score, as well as ICU stay, previous hospital admissions in the past year, and transfer from another hospital. Exposure to antibiotics was not identified as a statistically significant risk for the isolation of CSCF.

The results of the multivariable analyses of risk factors for CRCF are given in Table 3, and those for CSCF are given in Table 4. Multivariable logistic regression analyses demonstrated that exposure to the following antibiotics was significantly associated with nosocomial isolation of CRCF: imipenem (OR, 7.5; 95% CI, 1.2 to 45.4), broad-spectrum cephalosporins (OR, 6.9; 95% CI, 1.8 to 26.7), vancomycin (OR, 3.0; 95% CI, 1.2 to 7.4), and piperacillin-tazobactam (OR, 2.6; 95% CI, 1.1 to 6.2). Hospital length of stay ≥7 days (OR, 3.6; 95% CI, 1.3 to 10.2) and ICU stay prior to the isolation of CRCF (OR, 2.6; 95% CI, 1.1 to 6.2) were also found to be significant risk factors.

The independent risk factors for the isolation of CSCF were peripheral vascular disease (OR, 23.2; 95% CI, 4.3 to 124.6), AIDS (OR, 9.5; 95% CI, 1.6 to 55.5), cerebrovascular disease (OR, 4.2; 95% CI, 1.6 to 10.8), ICU stay (OR, 3.1; 95% CI, 1.8 to 5.4). Fluoroquinolones were found to be protective against the isolation of CSCF (OR, 0.26; 95% CI, 0.10 to 0.71). Because no antibiotics were found to be a statistically significant

TABLE 4. Multivariable analysis of risk factors for CSCF

Risk factor	Estimate[a]	Standard error[b]	P value	OR (95% CI)
Peripheral vascular disease	3.14	0.86	0.009	23.2 (4.3–124.6)
AIDS	2.25	0.9	0.01	9.5 (1.6–55.5)
Cerebrovascular disease	1.44	0.48	0.003	4.2 (1.6–10.8)
ICU stay	1.13	0.28	<0.0001	3.1 (1.8–5.4)
Fluoroquinolones (protective)	−1.35	0.52	0.0002	0.26 (0.10–0.71)

[a] Intercept, −1.71.
[b] Intercept, 0.20.

risk in the bivariate model, they were not included in the multivariable analysis.

DISCUSSION

To our knowledge, this is the only study that specifically assesses risk factors for the nosocomial isolation of CRCF or CSCF. Our study differs from previous analyses of risk factors for nosocomially acquired *Citrobacter* species in that a relatively large number of cases led to increased power (10, 24, 41, 44) and thus the ability to identify risk factors with lower frequencies of exposure. Another important advantage of this study is that it allows a simultaneous comparison of the risk factors for the isolation of antibiotic-resistant or -susceptible strains.

As discussed in previous studies, we believe that a refined control group selection process and the control of important confounding variables leads to greater validity of the risk factors identified (19–22, 27). As has been noted by Harris et al., a control group derived from an appropriate sampling method of the base population is preferred in studies of antibiotic-resistant pathogens that seek to identify factors causally related to antibiotic resistance. Measures of association are not meaningfully inferred from studies that rely on control patients that consist of patients with the susceptible forms of the organism. The choice of patients with susceptible organisms as a control group may lead to biased estimates of relative risk because of a distorted estimate of exposure frequency in the source population. The selection bias introduced by using control patients with susceptible organisms is likely to have the strongest impact on estimating the effect of exposure of antibiotics that are active against susceptible, but not resistant, organisms, which is often the exposure of interest. The reason for this particular bias is that treatment with active antibiotics likely inhibits the growth of susceptible organisms, therefore making this exposure less frequent among patients who are culture positive for susceptible organisms than among patients in the source population (22).

We found that imipenem, broad-spectrum cephalosporins, vancomycin, and piperacillin-tazobactam were the antibiotics associated with nosocomial isolation of CRCF. No antibiotics were associated with isolation of CSCF. The association of exposure to broad-spectrum antibiotics with the isolation of CRCF could suggest a role for the induction and/or derepression of resistance genes and elimination of commensal or competing organisms. Broad-spectrum antimicrobials have been identified as risk factors for other antibiotic-resistant pathogens, including multiresistant *Enterobacter* species and imipenem- and piperacillin-tazobactam-resistant *P. aeruginosa* strains (6, 20, 22, 29, 43).

Vancomycin was also found to be associated with the isolation of CRCF. The most likely explanation for this finding is that vancomycin was a marker of associated multiple antibiotic use in moribund patients. The fact that only 4.7% of the CRCF patients received vancomycin without concomitant gram-negative coverage lends credence to this hypothesis.

Infections caused by stably derepressed enzyme-producing species like CRCF appear to be most prevalent in seriously ill patients, such as those in the ICU (17). The association between ICU stay and length of hospitalization of ≥7 days as

strong independent risk factors is therefore not unexpected. These factors have been identified as risk factors in previous studies of antibiotic-resistant organisms (14, 18, 20, 22, 32, 33, 35). Others have found that infections due to *Citrobacter*, *Klebsiella*, *Enterobacter*, and *Serratia* as a group were associated with length of stay before infection and hospitalization in an ICU (44).

Length of stay of ≥7 days was an independent risk factor apart from antibiotic exposure. This factor may be linked to health care worker-to-patient and patient-to-patient transmission. It has been demonstrated that health care worker compliance with hand hygiene tends to be relatively low in settings with high-acuity patients such as the ICU (38). Another factor that may augment the nosocomial spread of antibiotic-resistant pathogens is "colonization pressure." Investigators have found that the number of patients already colonized on a unit may play an important role in determining how quickly noncolonized patients may acquire a resistant organism. Bonten et al. found that once the colonization pressure was 50% or higher, other variables, such as antibiotic use, hardly affected patient colonization with vancomycin-resistant enterococci (2). We were unable to directly assess the role of patient-to-patient transmission. However, not accounting for patient-to-patient transmission would likely bias toward the null hypothesis: that is, among patients who acquire the organism from other patients, the importance of antibiotics as causal components would be diminished. This did not appear to have a significant impact on the results of the present study, given the strong associations with antibiotics.

It is not surprising that comorbid conditions, such as peripheral vascular disease, AIDS, and cerebrovascular disease, were associated with the isolation of CSCF. It is known that *C. freundii* isolation has been particularly seen in patients with significant comorbidities (23, 30, 41).

Fluoroquinolones were found to be protective against the isolation of CSCF. They have been noted to have significant activity against most gram-negative pathogens, including nonresistant *Citrobacter* spp. (15). Ninety-four percent of the CSCF isolates were also susceptible to fluoroquinolones. In contrast, 56% of the CRCF isolates were resistant to fluoroquinolones. It follows that fluoroquinolone usage did not protect against the isolation of CRCF.

A limitation of the present study is that we do not know the molecular mechanisms that account for the resistance in our study isolates. In addition, because the control patients were not screened by active surveillance cultures for the presence of *C. freundii* colonization, it is possible that some of these patients might actually have been case patients. However, this type of misclassification bias would have made the groups of case patients and control patients more similar by including case patients in the control groups. The result would mean that our reported OR would actually be lower than the "true" OR. Stated another way, if we had a mechanism for correcting this misclassification, then the "true" OR would have been even higher than the ones reported in our study.

Antibiotic-resistant *Enterobacteriaceae* have been associated with longer hospital stays, greater use of additional antibiotics, and higher mortality (6, 11, 13, 20, 22). Among *C. freundii* isolates, resistance to broad-spectrum cephalosporins (ceftriaxone and ceftazidime), piperacillin, and piperacillin-tazobac-

tam has been reported to be between 39 to 48% and may be increasing (4, 36, 39, 40, 44). In this study, we have found that isolation of CRCF was significantly associated with recent exposure to broad-spectrum antibiotics and prolonged length of stay. Risk factors for CSCF were very different and did not include exposure to antibiotics, but did include comorbid conditions. Our data suggest that initiatives designed to reduce resistant gram-negative organisms should target the overuse of broad-spectrum antibiotics.

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